REMARKS

Claims 42 to 47, 50, and 53 to 120 are now pending in the application, new claims 90 to 120 having been added by the above amendment. Claims 79 to 88 were withdrawn by the Examiner as directed to a non-elected invention. Applicants have amended claim 58 to recite the range 0.005% to 0.05% carbon monoxide. Support for this amendment can be found in the specification, e.g., at page 10, line 14. Claim 60 has been amended to delete the terms "skin" and "lung." These terms are recited in new claims 90 and 95. New claims 91 and 92 depend from claim 60 and new claims 93 and 94 depend from claim 61. These new claims are supported throughout the specification, e.g., at page 5, lines 14 to 15. Claims 62 and 63 have been amended such that the amended claims do not recite the terms "brain," "spleen," and "skin." These terms are recited in new claims 96 and 97. As suggested in the Office Action, claims 65 to 69, 74, and 89 have been amended to recite administering to the patient a "therapeutically effective amount" of a composition comprising carbon monoxide. Claim 66 has also been amended to recite a method for reducing inflammation associated with a wound, and claim 68 has been amended to recite a method of treating inflammation associated with arthritis. New dependent claims 98 to 104, 106, 108, 110, 112 to 114, 116, 118, and 120 recite that the composition recited in various independent claims is administered as an inhaled gas. New dependent claims 105, 107, 109, 111, 115, 117, and 119 recite that the patient recited in various independent claims is a human. Claims 58, 73, 78, 83, and 88 have been amended to replace the term "comprises" with "contains." Support for all of these amendments can be found throughout the specification. The amendments and new claims add no new matter to the present application.

Change of Inventorship

As applicants indicated in the Supplemental Preliminary Amendment dated July 17, 2002, applicants' representative has determined that Patty Lee was erroneously named as a co-inventor on the present and parent application. Applicants submit herewith a Request to Correct Inventorship and all papers required under 37 C.F.R. §1.48(a) to correct this error.

Withdrawn Rejections

While the examiner did not explicitly withdraw previous rejections, applicants assume that all prior rejections not reasserted in the present Office Action are withdrawn. Thus, applicants acknowledge the withdrawal of the following rejections:

(a) the rejection of claims 42 to 64, 67, and 69 for an alleged lack of enablement;

(b) the rejection of claims 42 to 64 as allegedly indefinite;

(c) the rejection of claim 69 as allegedly anticipated by and/or obvious in view of Abidin et al. (*Kosmicheskaya Biologiya i Aviakosmicheskaya Meditsina* 6:63-67 (1978)); and

(d) the rejection of claims 42 to 47 and 50 to 67 as allegedly obvious over Eschwey (WO 98/08523) in view of Choi et al. (*Am. J. Resp. Cell Mol. Biol.* 15(1):9-19 (1996)), Lefer et al. (*Methods and Findings in Experimental and Clinical Pharmacology* 15(9):617-622 (1993)), Vassalli et al. (*Eur. Resp. J.* 12, Supp. 28, 237s (1998)), and Abidin et al.

I. Rejections under 35 U.S.C. § 112, first paragraph

Claims 65, 66, and 68 were rejected under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement because, according to the Office Action (at page 3):

> The prior [sic] of record does not appear to show prevention of inflammation secondary to sepsis, promotion of wound healing or arthritis, as such, it does not appear from the prior art that one of ordinary skill in the art could predict that administration of carbon monoxide would be effective in preventing inflammation secondary to sepsis, promoting wound healing or arthritis.
>
> Further, the Specification does not appear to provide any working examples in which inflammation secondary to sepsis was prevented, wounds were healed or arthritis was treated. It appears that inflammation would be present if sepsis is present, as such, it is uncertain how one of ordinary skill in the art could prevent inflammation is [sic] sepsis is already present.

Applicants believe that the claims are fully enabled as filed. However, in the interest of moving the present claims toward allowance, applicants have amended claim 65 such that it no longer recites the term "prevent." As amended, claim 65 now more broadly recites a method of reducing inflammation secondary to sepsis, thereby covering, for example, both (a) situations in

which symptoms of inflammation are already apparent in the patient, and (b) situations in which the patient is not yet exhibiting such symptoms but either in fact is suffering from sepsis, or is considered to be at risk of sepsis. In view of the Office Action's above-quoted language, applicants believe that this amendment obviates the present rejection with respect to claim 65.

Further, applicants respectfully point out that the specification provides a working example (at pages 25 to 37) indicating that carbon monoxide would be effective to reduce inflammation secondary to sepsis. There, applicants demonstrated that carbon monoxide acts as a potent anti-inflammatory agent, both *in vitro* and *in vivo,* using a model of *Escherichia coli* lipopolysaccharide (LPS)-induced inflammation. LPS is a bacterial cell wall component considered largely responsible for the inflammatory symptoms of sepsis. Thus, applicants submit that the specification is fully enabling for the method recited in amended claim 65.

Applicants have also amended claims 66 and 68 in order to clarify their intended scope. As amended, claim 66 recites a method for reducing inflammation associated with a wound. Similarly, claim 68 has been amended to recite a method of treating inflammation associated with arthritis.

Arthritis and wounds are known to involve inflammation. As applicants pointed out in this and their previous Reply, the specification provides working examples demonstrating that carbon monoxide can, in fact, be used to reduce inflammation. It is well established that arthritis and wounds involve inflammation. To corroborate this assertion, applicants submit herewith copies of the following two journal articles: Taylor ("Anti-TNF Therapy for Rheumatoid Arthritis and Other Inflammatory Diseases," Molecular Biotechnology 19(2):153-68 (2001) (designated on the accompanying Information Disclosure Statement (IDS) form PTO-1449 as "AN"); and Hayes ("A Review of Modern Concepts of Healing of Cutaneous Wounds," J. Dermatol. Surg. Oncol. 3(2):188-93 (1977) (designated on the accompanying IDS form PTO-1449 as "AJ"). Applicants point out that Taylor suggests treating rheumatoid arthritis with anti-inflammatory agents (see, e.g., Taylor at page 165, left column). Thus, in view of the amendments and comments presented above, applicants respectfully request that the present rejection be reconsidered and withdrawn.

II. Rejections under 35 U.S.C. § 112, second paragraph

Claims 65 to 69, 74, and 89 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite because they did not recite the term "therapeutically effective amount." As applicants indicated in their previous Reply, applicants believe that the claims need not recite this term to be in compliance with 35 U.S.C. § 112, second paragraph, and respectfully submit that the claims are definite as filed. However, in the interest of moving the present claims toward allowance, applicants have amended claims 65 to 69, 74, and 89 as requested in the Office Action. As amended, these claims recite administering to a patient a "therapeutically effective amount" of a composition comprising carbon monoxide. Thus, applicants respectfully request that the present rejection be withdrawn.

Claims 42 to 47, 50, 53 to 78, and 89 were rejected under 35 U.S.C. § 112, second paragraph for allegedly failing to set forth the subject matter that applicants regard as their invention. The Office Action states (at page 4):

> Evidence that claims 42-78,89 fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in Paper No. 13 filed 2/3/2003. In that paper, applicant has stated "none of the publications cited in the Office Action, singly or in combination, teaches or suggests administering inhaled carbon monoxide gas as a therapeutic agent to treat the diseases and conditions recited in the pending claims" (pg. 20), and this statement indicates that the invention is different from what is defined in the claims(s) because the claims do not indicate that the carbon monoxide is administered by inhalation.

Based on the above-quoted language, the Office's position appears to be that the claims must recite administering carbon monoxide to patients via inhalation in order to be in compliance with 35 U.S.C. § 112, second paragraph.

As an initial matter, applicants submit that, contrary to the above-quoted statement, claims 53 to 55 do explicitly require that the carbon monoxide-containing composition be administered as an inhaled gas. Thus, the present rejection is moot with respect to these claims. With respect to claims 42 to 47, 50, 56 to 78, and 89, applicants respectfully traverse this rejection and submit that the claims are in full compliance with 35 U.S.C. § 112, second paragraph, for the reasons discussed below.

The Office Action quotes a sentence from applicants' reply to the Office Action dated July 30, 2002, as alleged evidence that the claims do not set forth the subject matter of the invention. Applicants respectfully submit that the sentence is quoted out of context. The sentence merely describes the shortcomings of the publications cited in the previous Office Action as prior art, several of which publications discuss inhalation of carbon monoxide gas (see, e.g., Abidin et al., Kosmicheskaya Biologiya i Aviakosmicheskaya Meditsina (1978) 6:63-67, Vassalli et al. (Eur. Resp. J. 12, Suppl. 28, 273s (1998), and WO 98/08523 ("Eschwey")). The point being argued did not hinge on the "inhaled" aspect, and indeed could not have since the cited art did mention inhalation of carbon monoxide. Clearly the point being made by applicants was that the prior art did not disclose the use of carbon monoxide as a therapeutic agent to treat the diseases and conditions recited in the claims. Furthermore, nowhere does the present specification limit the invention to administering carbon monoxide compositions by inhalation. The originally filed claims recited no such limitation. In fact, applicants' claims filed in the Supplemental Preliminary Amendment dated July 17, 2003, specifically recite administration by inhalation in dependent claims (see, e.g., claims 53, 54, and 55), indicating, contrary to the Office Action's assertion, that applicants regarded inhalation to be only one embodiment of the present invention.

At the time the application was filed, applicants recognized, as would any skilled practitioner at that time, that gaseous compositions could be administered to patients in any number of ways. Modes of administration of gases to patients other than by inhalation were well known in the art. For example, extracorporeal membrane oxygenation (ECMO) was routinely used to administer gases to patients (see, e.g., Peek et al., Chest 112: 759 – 764 (1997), designated on the accompanying IDS form PTO-1449 as "AM"). Art that is already of record in this application establishes this point as well. For example, Eschwey (cited in the Office Action dated July 30, 2002) discusses administering hydrogen-containing medicaments in the form of, e.g., capsules, foams, solutions, and ointments (see Eschwey, abstract).

Accordingly, applicants submit that the claims correspond in scope with what they regard as the invention, and that they are therefore in full compliance with 35 U.S.C. § 112, second

paragraph. The claims particularly point out and distinctly claim the present invention as required under the statute. Thus, applicants respectfully request that the present rejection be reconsidered and withdrawn.

Claim 65 was also rejected as allegedly indefinite for lack of antecedent basis for the phrase "reduce or prevent inflammation." Applicants have amended the preamble of claim 65 to recite "a method of reducing inflammation secondary to sepsis in a patient," thus obviating the present rejection. Accordingly, applicants request that the present rejection be withdrawn.

New Rejections Under 35 U.S.C. §102/103

Claim 61 was rejected as allegedly anticipated by an abstract by Campbell (*Brit. J. Exp. Path.*, 15(5):287-294 (1934)). A copy of the full-text version of Campbell is provided with the accompanying IDS. The Office Action states (at page 5):

> Campbell teaches that inhalation of carbon monoxide retarded development of cancer of the skin and primary adenoma of the lungs in mice.

Applicants traverse this rejection because claim 61 recites treating human cancer patients, not mice. Thus, Campbell does not anticipate claim 61. Applicants respectfully request that the present rejection be reconsidered and withdrawn.

Claims 60 and 61 were rejected as allegedly obvious over an abstract by Maxwell et al. (*J. Pharmacol.*, 49:270-282 (1933)) in view of Campbell. A copy of the full-text version of Maxwell is provided with the accompanying IDS. The Office Action states (at page 6):

> Maxwell et al. teach that exposure of animals bearing transplantable tumors to carbon monoxide resulted in a decrease in the rate of tumor growth.
>
> * * *
>
> The difference between the claimed invention and the prior art is that the prior art does not expressly disclose the treatment of cancer in a human patient by administering carbon monoxide. However, the prior art amply suggests the same as it is known that it is effective in the treatment of cancer in animals. As such, it would have well [sic] within the skill of and [sic] one of ordinary skill in the art would have be [sic] motivated to use the same in humans with the expectation that inhaled carbon monoxide would be effective in treating cancer in humans.

Applicants agree with the above-quoted passage from the Office Action that neither Campbell nor Maxwell expressly discloses treating human patients using carbon monoxide. However, applicants do not agree with the assertion that these publications "suggest" such treatments for humans (or any other animal), and submit that they would not have provided the requisite motivation to treat any cancer patient with carbon monoxide. Indeed, as elaborated below, each of the cited references teaches away from using carbon monoxide as a therapeutic agent.

Campbell described an experiment in which mice were exposed over a long period of time to dust obtained from tarred roads, a substance known to cause warts and cancer of the skin in mice (page 287). Some of the dusted mice breathed air containing 0.2 to 0.3 percent carbon monoxide gas, while the control mice breathed air without the carbon monoxide (pages 288 to 289). Campbell reports that at the time the first wart appeared on a mouse, only 52% of the carbon monoxide-treated mice were still alive, compared to 77% of the air-breathing mice (page 290). According to Campbell (at page 290), "[t]his is to be expected as an effect of carbon monoxide."

No so-called "treatment" that produces substantially more deaths at any time point than the condition being treated could possibly be deemed of interest to the medical community. A physician reading Campbell would understand that inhaling carbon monoxide would do more harm than good, and should not even be tried in a medical treatment. Thus, Campbell emphatically teaches away from the use of CO to treat cancer (or any other conditions, for that matter) in any animal.

Maxwell (at page 270) indicates that the authors performed the study to "study the effect upon tumor growth of the administration of various substances known to produce severe blood and tissue anoxias," carbon monoxide being one of those substances. Maxwell (at page 271) states that in exposing mice to carbon monoxide at a concentration of 500 ppm and gradually increasing the concentration to 2000 ppm, they sought to keep the mice "at all times in a condition of severe anoxia as evidenced by symptoms of weakness and prostration." Furthermore, Maxwell reported on page 278 that "the action upon tumor growth apparently

consists only in retardation of growth without actual destruction of cancer cells." Given such statements, Maxwell can't be said to have taught a clinically useful approach to treating cancer. One of ordinary skill, reading Maxwell, would have understood that to achieve any reduction in tumor growth, it would have been necessary to use enough carbon monoxide to leave the patient in "severe anoxia as evidenced by symptoms of weakness and prostration," a condition unlikely to be acceptable as a clinical treatment in any animal, much less humans. Furthermore, even such a drastic treatment does not destroy the cancer. According to Maxwell, all it does is retard its growth. Thus, one reading Maxwell would have been dissuaded from investigating carbon monoxide as a possible therapeutic agent for treatment of cancer. Certainly Maxwell did not suggest it. Given the harmful effects described by Campbell and Maxwell, a skilled practitioner would have had no reason to expect such treatments to be clinically appropriate, and indeed, it appears that neither Campbell nor Maxwell conducted their experiments with the intent of developing carbon monoxide as a clinically useful treatment. If they had such treatment in mind, they would have tested less harmful doses of the gas. Thus, applicants respectfully submit that neither Campbell nor Maxwell, singly or in combination, renders obvious claims 60 or 61 (or any of the new claims reciting methods of treating cancer, including claims 90 to 95, 100, 101, 116, and 117), and request that the present rejection be reconsidered and withdrawn.

Although the terms "lung" and "skin" were deleted from claim 60, they are recited in new claim 90. Claim 90 recites a method of treating lung or skin cancer in a patient and specifies that the concentration of carbon monoxide in the composition is about 25 to about 750 ppm. The terms "lung" and "skin" are also recited in new claim 95, which depends from claim 61 and recites a method of treating lung or skin cancer in a human patient. New claims 93 and 94 also depend from claim 61, limiting the composition to specific concentration ranges of carbon monoxide (about 50 to about 500 ppm and about 25 to about 750 ppm, respectively). Applicants respectfully submit that neither Campbell nor Maxwell, singly or in combination, renders new claims 90 and 93 to 95 obvious for the reasons discussed above with respect to claims 60 and 61.

Claims 57 to 59 and 62 to 65 were provisionally rejected as allegedly anticipated by an abstract by Chapman et al. (Am. J. Resp. Crit. Care Med. 159(3):A218 (1999); hereinafter "Chapman"). A copy of the full-text Chapman abstract is provided with the accompanying IDS. Applicants submit that Chapman is not prior art citable against claims 57 and 59 and amended claims 58, 62, 63, and 65. Applicants respectfully point out that the present application claims priority from U.S. Application Serial No. 09/538,788, which has a filing date of March 30, 2000, and from Provisional Application Serial No. 60/127,616, filed on April 1, 1999. Claims 57 and 59 and amended claims 58, 62, 63, and 65 are fully supported by the disclosure of the provisional application, e.g., at the first page of the application, at lines 2 to 4, 18 to 24, and 43 to 41, and at the fourteenth page (labeled as page 12 in the provisional application), lines 18 to 21. These claims are therefore entitled to a priority date of April 1, 1999. Applicants submit herewith an *In re* Katz Declaration signed by Leo E. Otterbein establishing that Jeff T. Chapman and Jack A. Elias made no inventive contribution to the present application. Chapman reports the inventors' own work and was published less than one year before the April 1, 1999 priority date. It therefore is not prior art under any subsection of 35 U.S.C. §102 with respect to these claims.

With respect to claim 64, applicants respectfully traverse this rejection. The Chapman abstract describes an investigation of the role of carbon monoxide gas in a mouse model for asthma. Chapman does not describe, or even suggest, using carbon monoxide to treat patients (e.g., human patients) for any type of inflammation of the kidney, spleen, or skin. Since Chapman does not describe or suggest such treatments, Chapman does not anticipate claim 64.

For the reasons discussed above, applicants request that the provisional rejection of claims 57 to 59 and 62 to 65 be reconsidered and withdrawn.

CONCLUSION

Applicants submit that all claims are in condition for allowance, which action is requested. Enclosed is a check for $950 for the Petition for Extension of Time fee for a three-month extension. Please apply any other charges or any credits to Deposit Account No. 06-1050, referencing Attorney Docket Number 13681-003002.

Respectfully submitted,

Date: Nov. 19, 2003

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